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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION SHEET PTO6-303

Continuation of 5. The rejection of claims 8-11 under 35 U.S.C. 112, first paragraph (enablement), is moot in view of Applicant's cancellation of the claims in the reply filed 1/11/2010. The rejection of claims 8-11 under 35 U.S.C. 112, first paragraph (written description), is moot in view of Applicant's cancellation of the claims in the reply filed 1/11/2010.

Continuation of 7 and 11. Claims 1-3 and 15-18 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for the reasons of record.

Applicant's arguments filed 1/11/2010 have been fully considered but they are not persuasive.

It is noted that Applicant asserts that the Examiner and Applicant's attorney agreed that removal of the language "mRNA transcribed therefrom or protein encoded thereby" in conjunction with the remarks submitted regarding primer/probe design would be sufficient to overcome the outstanding enablement rejection.

Contrary to Applicant's assertions, the Examiner and Applicant's attorney did not come to such an agreement. Ways in which the rejections of record under 35 U.S.C. 112, first paragraph, may be overcome were discussed; however, no agreement was reached.

At the paragraph bridging pages 7-8, the reply notes that the previously pending claims allegedly lacked enablement due to the recitation of "SEQ ID NO: 36." Specifically, the

sequence of SEQ ID NO: 36 is an EST with insufficient information to identify the level of mRNA transcribed from or protein encoded by SEQ ID NO: 36. The response asserts that the removal of "mRNA transcribed therefrom or protein encoded thereby" from the claims has rendered this aspect of the enablement-based rejection moot.

This argument is found persuasive with respect to the detection of protein encoded by SEQ ID NO: 36. The amendment to the claims now limits the method to assaying expression of the nucleic acid sequences set forth in SEQ ID NOs: 29-38. However, the claims still require the detection of mRNA expression by assaying the level of expression of the nucleic acid sequences set forth in SEQ ID NOs: 29-38. These arguments are not found persuasive with respect to the detection of expression of the nucleic acid sequence of SEQ ID NO: 36 for the reasons of record and the reasons discussed below.

The response asserts that the detection of expression of the nucleic acid sequence of SEQ ID NO: 36 is enabled for the following reasons: (1) the response asserts that the probes on the Affymetrix array used by Applicants to detect the expression of W26469 (SEQ ID NO: 36) are known in the art; and (2) the skilled artisan would be fully capable of designing their own primers and probes to W26469 (SEQ ID NO: 36) based upon the sequence information available in GenBank.

(1) Assertion that the probes on the Affymetrix array were known in the art

The response notes that the specification does not disclose the probe sequences on the Affymetrix array that were used to detect expression of SEQ ID NO: 36. However, the response asserts that the probe sequences are available online at the Affymetrix web site. The response

provides the probes on the HG-U95av2 microarray disclosed as set 31377_r_at in Table 1 of the specification.

These arguments are not found persuasive. The Affymetrix 31377_r_at probe set was not well known in the art at the time the invention was made. A search of PubMed for "31377_r_at" returns no citations (see the search history provided in Appendix I). A search of Google Scholar and EAST returns the publication of the present application (see the search histories provided in Appendices II and III, respectively). Thus, the probe sequences do not appear to have been available in a printed publication prior to the effective filing date of the present application. Furthermore, the presence of the sequences in an online database cannot substitute for the disclosure of the sequences when the sequences are essential to the practice of the claimed invention.

(2) Assertion that the skilled artisan could design primers and probes to SEQ ID NO: 36

The response asserts that the skilled artisan would be fully capable of designing their own primers and probes to W26469 based upon the sequence information in GenBank (also present in SEQ ID NO: 36). The response notes that GenBank discloses 350 known nucleotides for W26469 (and a long string of unknown nucleotides designated "N"). The response asserts that regardless of the presence of some unknown nucleotides in the 350 known nucleotide sequence – a skilled artisan would have no difficulty in designing a primer, primer set, or probe from this sequence for use in Northern blotting, microarray hybridization, PCR, and other hybridization techniques. First, the response notes that the Office has only shown that small portion of W26469 can hybridize to various genomic sequences. Second, the response asserts that there are well-known established and accepted methods to routinely optimize and empirically identify the

best hybridization conditions for a particular target sequence and selected primer/probe. The response goes on to provide examples of conditions that may be optimized and programs that may be used to design primers, for example. Third, the response asserts that even if one were not able to use a traditional 20-25 base pair primer designed from the GenBank sequence, one could surely employ the entire known portion of the W26469 sequence to obtain high specificity in various hybridization techniques.

These arguments are not found persuasive. The sequence of SEQ ID NO: 36 is as follows:

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NNNNNNNNNNNNTNNTNNNNCGGNGGNCTACCCTNCATACTTAGTTGTGAGATCCATCCCCTGGCTTCAT
TCCCTGAACTGGCTTTAGNAACNCTGGCAGTCTAGCTTATAACCCCCAGGCTGACTAGAGAACTCAAGGT
AAAAGCAGCCCAAGAAAAACAGACCAACAGAAAAGCAATGAGAGAAAGGATGAAGGTTCCCTNCTCGATG
ATCCATTAANTGGAAGAGTAACCCAAGAAAACATCATGGANTCCAAGANTCAGTGGATCCAGCACAANAA
GGNGGNAAAGGGNNATTCAGCTNGGTCTTANCAGGTGACTGTCAAANNNNGGNNTNNNCCCAGNNTGNNC
TGNTCAANNNNNNNTNNNNCAGNNTNNNNTNGNCANNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNGG.
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As discussed in the rejection of record (e.g., page 7 of the action mailed 11/18/2009), the specification teaches that there was insufficient sequence data to design TaqMan primers and probe for quantitative RT-PCR (e.g., Table 3). Applicant's own post-filing art (Scherer et al. Transplantation, Vol. 75, No. 8, pages 1323-1330, April 2003, of record), states, "the **known DNA sequence was insufficient to design functional** TaqMan primer-probe sets (W26469:32f4)" (emphasis added; see page 1326, right column, 1st full paragraph). While it would have been within the skill of the art to use the available sequence from the GenBank record (W26469) in combination with known techniques or computer programs to design primers and probes to the sequence of W26469 (SEQ ID NO: 36), the ability of those primers

and probes to function is unpredictable. In the post-filing art (Scherer et al. 2003), Applicant discloses primers and probes selected for W26469 (e.g., page 1326, left column, lines 4-6). However, the primers and probes were not functional (e.g., page 1326, right column, 1st full paragraph). The inability to provide functional primers and probes may relate to the poor quality sequence data provided by GenBank Accession No. W26469 (SEQ ID NO: 36), e.g., note the sequence ambiguities "N" throughout the sequence. Given that no functional primers and probes could be found, it would require undue experimentation for the skilled artisan to do so.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. The prior art does not teach primers and probes to SEQ ID NO: 36, and there is no convincing evidence on the record that one could design primers and probes that function to reliably detect expression of SEQ ID NO: 36 to assess the risk of chronic rejection. Therefore, the claims stand rejected under 35 U.S.C. 112, first paragraph.

Claims 1-3 and 15-18 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons of record.

Applicant's arguments filed 1/11/2010 have been fully considered but they are not persuasive.

It is noted that Applicant asserts that the Examiner and Applicant's attorney agreed that removal of the language "mRNA transcribed therefrom or protein encoded thereby" in

conjunction with the remarks submitted regarding primer/probe design would be sufficient to overcome the outstanding written description rejection.

Contrary to Applicant's assertions, the Examiner and Applicant's attorney did not come to such an agreement. Ways in which the rejections of record under 35 U.S.C. 112, first paragraph, may be overcome were discussed; however, no agreement was reached.

The response asserts that to detect the level of expression of SEQ ID NO: 36, a skilled artisan need only to look to GenBank (and the sequence listing provided for the instant application) to recognize that Applicants possessed the currently claimed methods. The response asserts that the sequence of SEQ ID NO: 36 would allow a skilled artisan to design probes and primers useful in various hybridization techniques and PCR methods to measure the level of SEQ ID NO: 36 from a patient. The response notes that Applicants did use microarray technology with W26469 probes to assay the level of W26469 in samples.

These arguments are not found persuasive. The specification does not disclose the probes on the Affymetrix HG-u95av2 array, and the probe sequences do not appear to be well known in the art at the time the invention was made (see the search histories in Appendices I-III). Accordingly, the probe sequences are not well known in the art and have not been disclosed in a printed publication. Applicant cannot rely on an online database to provide essential subject matter. Further, the evidence of record indicates that it was not within the skill of the art to design primers and probes to the sequence of SEQ ID NO: 36. The specification teaches that there was insufficient sequence data to design probes and primers (e.g., Table 3). Applicant's own post-filing art teaches that no functional primers and probes could be designed to assay the expression of W26469 (SEQ ID NO: 36) (Scherer et al. Transplantation, Vol. 75, No. 8, pages

1323-1330, April 2003, of record; e.g., page 1326, right column, 1st full paragraph). The EST clone was not available to one of skill in the art (GenBank Accession No. W26469, of record). Thus, one would not be able to obtain the clone to provide more reliable sequence data for the design of probes and primers. Accordingly, Applicants were not in possession of the reagents necessary to detect the expression of SEQ ID NO: 36.

The portion of the rejection directed to the description of reagents necessary to detect protein expression of a protein encoded by SEQ ID NO: 36 has been rendered moot by the entry of the amendment filed 1/11/2010.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. 112, first paragraph.

Continuation of 13. Other: Applicant's reply has overcome the following objection(s): objection to the specification.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636